REMARKS & CONCLUSION

The above-listed claim amendments along with the following remarks are fully responsive to the Final Office Action of April 4, 2006. Claims 28-32 are pending. Claims 28-30 are amended. No new matter is added by the Amendment.

Objections

The abstract was objected to as not commencing on a separate sheet in accordance with 37 CFR 1.52(b)(4). With this Amendment, the amended replacement Abstract, beginning on a separate page, is attached. No new matter is added with this replacement abstract.

Claim Rejections – 35 U.S.C. § 112, 2nd paragraph

Claims 28-32 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite. In particular, the Office Action indicated that claim 28 is indefinite because it is not known whether both heavy and light chain variable domains of a monoclonal antibody are humanized and whether the heavy and light chain variable domains of the monoclonal antibody to be humanized are compared to only the heavy chain variable domain or only the light chain variable domains of two or more human antibodies.

Claim 28 is amended to recite amino acid sequences of "variable domains," which indicates that the variable domains of both the heavy and light chains are humanized by comparing them to their corresponding variable domains of both the heavy and light chains in two or more human antibodies.

Applicants respectfully request withdrawal of this rejection.

Claim Rejections – 35 U.S.C. § 112, 1st paragraph

Claims 28-32 have been rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. In particular, the Office Action asserted that there is inadequate disclosure for selecting framework regions of two or more human monoclonal antibodies wherein each framework region has a sequence identity of approximately 75 to 92.3 %. The Office Action also suggested that there is insufficient written support for "human monoclonal antibodies." Applicants respectfully traverse this rejection.

Claim 28 recites a method of designing amino acid sequences of variable domains of a humanized monoclonal antibody. Applicants point out that the method is based on sequence homology between the framework regions of the monoclonal antibody to be humanized and those of selected human antibodies. See paragraph [0043], Example 1 and Figure 1. The highest frequencies of residue identities between the variable domains of a non-human monoclonal antibody to be humanized is determined by searching and comparing sequences with human antibodies identified in databases, such as Kabak and PDB. Because the selection criteria is based purely on sequence homology, the human framework regions for the heavy and light chains can come from different human antibodies. Furthermore, even framework regions in a heavy or light chain can come from different heavy or light chains of different human antibodies. Support for this approach is found in Example 1 and Figure 1, where the framework regions of the variable domains of the heavy chain are selected from two different human antibodies, namely EU and NEW. The framework regions of the variable domains of the light chain are from REI.

The Office Action also asserted that there is inadequate written description support for the range of residue identities. The specification at paragraph [0043] clearly discloses the residue identity range of 75-92.3% for both the heavy and light chains, providing explicit written description support for that range.

To expedite prosecution, however, Applicants have amended claim 28 to recite a residue identity of 69% or higher for the light chain and 62.5% or higher for the heavy chain. Support for this amendment may be found at least in Example and Figure 1. Furthermore, the Office Action acknowledges that the present application supports the amended frequency of residue identities. See Office Action at page 6, lines 17-19.

Applicants respectfully submit that a skilled artisan would know that success of humanization depends on the sequence homology between the monoclonal antibody to be humanized and the human framework regions from human antibodies selected for humanization. One of skill in the art would recognize that the higher the homology, the more successful the method of humanizing a non-human monoclonal antibody. Thus, the high frequency of residue identities, 75-92.3%, would likely result in successful humanized design. Applicants have shown in Example 1 that an amino acid residue identity range lower than 75-92.3% in some framework regions also resulted in successful humanization. The skilled artisan reading

Example 1 would reasonably believe that if a sequence identity of less than 75-92.3% may, in some cases, result in a usable humanized antibody, then a higher range would be even more likely to result in a usable humanized antibody. Thus, Example 1 and Figure 1 do not contradict the disclosed range of 75-92.3%, but in fact further support this disclosed range.

As presently amended, the claims recite that the selection of the amino acid sequences is from "human antibodies" and not "human monoclonal antibodies." Support for this amendment can be found through the Specification and at least at paragraphs [0043] and Example 1.

Thus, the present Specification and its teachings place the public in possession of the claimed method. Hence, withdrawal of this rejection is respectfully requested.

Conclusion

In light of the amendments and remarks herein, Applicants respectfully request entry of this paper. If there are any remaining questions, the Examiner is requested to contact the undersigned at the number listed below.

Respectfully Submitted,

By: _____

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M2:20797573.01

In the Abstract:

An amended replacement Abstract is attached at the end of this paper.